J Atheroscler Thromb, 2018; 25: 359-373.
http://doi.org/10.5551/jat.41533

Original Article

Factors Associated with Intima-Media Complex Thickness of the Common Carotid Artery in Japanese Noncardioembolic Stroke Patients with Hyperlipidemia: The J-STARS Echo Study

Shinichi Wada[1], Masatoshi Koga[2], Kazunori Toyoda[1], Kazuo Minematsu[1], Masahiro Yasaka[3], Yoji Nagai[4], Shiro Aoki[5], Tomohisa Nezu[5], Naohisa Hosomi[5], Tatsuo Kagimura[6], Hideki Origasa[7], Kenji Kamiyama[8], Rieko Suzuki[9], Toshiho Ohtsuki[5, 10], Hirofumi Maruyama[5], Kazuo Kitagawa[11], Shinichiro Uchiyama[12] and Masayasu Matsumoto[5, 13], on behalf of the Japan Statin Treatment Against Recurrent Stroke (J-STARS) Echo Study Collaborators

[1]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[2]Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan
[3]Department of Cerebrovascular Medicine and Neurology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan
[4]Center for Clinical Research, Kobe University Hospital, Kobe, Japan
[5]Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan
[6]Foundation for Biomedical Research and Innovation, Translational Research Informatics Center, Kobe, Japan
[7]Division of Biostatistics and Clinical Epidemiology, University of Toyama Graduate School of Medicine and Pharmaceutical Science, Toyama
[8]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, Japan
[9]Department of Neurology, Kyorin University Hospital, Tokyo, Japan
[10]Stroke Center, Kinki University, Osaka, Japan
[11]Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan
[12]Clinical Research Center, International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Hospital and Sanno Medical Center, Tokyo, Japan
[13]Japan Community Healthcare Organization (JCHO) Hoshigaoka Medical Center, Osaka, Japan

***Aims*: There may be ethnic differences in carotid atherosclerosis and its contributing factors between Asian and other populations. The purpose of this study was to examine intima-media complex thickness (IMT) of the carotid artery and associated clinical factors in Japanese stroke patients with hyperlipidemia from a cohort of the Japan Statin Treatment Against Recurrent Stroke Echo Study.**

***Methods*: Patients with hyperlipidemia, not on statins, who developed noncardioembolic ischemic stroke were included in this study. Mean IMT and maximum IMT of the distal wall of the common carotid artery were centrally measured using carotid ultrasonography. Significant factors related to mean IMT and maximum IMT were examined using multivariable analysis.**

***Results*: In 793 studied patients, mean IMT was 0.89 ± 0.15 mm and maximum IMT was 1.19 ± 0.32 mm. Age (per 10 years, parameter estimate = 0.044, $p < 0.001$), smoking (0.022, $p = 0.004$), category of blood pressure (0.022, $p = 0.006$), HDL cholesterol (per 10 mg/dl, −0.009, $p = 0.008$), and diabetes mellitus (0.033, $p = 0.010$) were independently associated with mean IMT. Age (per 10 years, 0.076, $p < 0.001$), smoking (0.053, $p = 0.001$), HDL cholesterol (−0.016, $p = 0.036$), and diabetes mellitus (0.084, $p = 0.002$) were independently associated with maximum IMT.**

***Conclusion*: Baseline mean and maximum values of carotid IMT in Japanese noncardioembolic stroke patients with hyperlipidemia were 0.89 ± 0.15 mm and 1.19 ± 0.32 mm, respectively, which were similar to those previously reported from Western countries. Age, smoking, hypertension, HDL cholesterol, and diabetes mellitus were associated with mean IMT, and those, except for hypertension, were associated with maximum IMT.**

Key words: Carotid artery, Dyslipidemia, Intima-media thickness, Statin, Stroke prevention, Ultrasound

Background and Purpose

Carotid ultrasound is used to measure intima-media complex thickness (IMT) as a marker of atherosclerosis, as well as a risk factor for cardiovascular events[1-4]. In Western countries, IMT has been reported to be attenuated by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) that can decrease cholesterol biosynthesis in the liver[5-9]. However, the effect of HMG-CoA reductase inhibitors on IMT has not been well established in Japan. The Japan Statin Treatment Against Recurrent Stroke (J-STARS) trial is a multicenter, prospective, randomized, open-label, parallel group trial of secondary stroke prevention using pravastatin 10 mg/day (usual dose in Japan) in the stroke patients with hyperlipidemia. The aim of this trial is to examine whether pravastatin prevents stroke recurrence in Japanese patients with noncardioembolic ischemic stroke. The J-STARS Echo Study is a substudy of the J-STARS study that aims to explore the pleiotropic effects of regular statin therapy on the changes of carotid atherosclerosis assessed by ultrasonography. Baseline characteristics, baseline mean and maximum IMTs, and the atherosclerosis factors correlated with the baseline mean and maximum IMTs were examined.

Patients and Methods

Study Design

The study design methods of the J-STARS Echo Study were described elsewhere[10, 11]; thus, the methods are stated briefly here. The protocol and informed consent form of the present substudy were approved by the institutional review board of each center, and written informed consent was obtained from each patient together with the main trial. The J-STARS Echo Study is registered with ClinicalTrials.gov (NCT00361530) and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (C000000212) separately from J-STARS (NCT00221104, UMIN C000000207).

Patient Population

Patients from 61 hospitals with certified sonographers in the J-STARS Echo Study were enrolled in this substudy. The inclusion criteria for the main trial were as follows: (1) age between 45 and 80 years; (2) clinical diagnosis of noncardioembolic ischemic stroke developing within the preceding month to 3 years; and (3) history of hyperlipidemia with serum total cholesterol levels maintained between 4.65 and 6.21 mmol/L (180 and 240 mg/dL), without the use of statins. Additional exclusion criteria for the main trial have been described in elsewhere[10, 11].

Randomization and Treatment

The patients were enrolled through a web-based registration and follow-up system for the main trial. Patients assigned to the pravastatin group received pravastatin 10 mg/day, and those in the control group received no statin treatment, although other drugs were administered when necessary.

Carotid Ultrasonography

Carotid ultrasonography was performed in each participating institute by well-trained physicians or laboratory technicians who were certified as expert examiners for this study. Baseline examinations were performed at the time of enrollment in the study. The examination methods have been described in elsewhere[11].

Carotid IMT Measurements

Videotapes or CD-Rs of the ultrasonography were sent to the J-STARS ECHO office for assessment, including kinetic measurements. All measurements were performed by a well-trained technician who was blinded to all clinical information.

Carotid IMT measurement methods have been described in elsewhere[11]. Still images (640 × 480 pixels) were imported from the videotapes or CD-Rs via a video port with a resolution of 1 pixel corresponding to 0.1 mm (**Fig. 1**). All still images were then imported into an IMT measurement software (IntimaScope; Mediacross, Tokyo, Japan), and IMT was measured on the distal wall in a continuous 2-cm section on the central side of the common carotid artery (CCA) bifurcation[12]. This software was programmed to automatically draw 2 lines at the junctions of the intima-media complex with the blood and the adventitia, and it was capable of measuring distances down to 0.01 mm[13]. Mean and maximum values of IMT in a 2-cm continuous section of the distal CCA were calculated automatically, and plaque thickness was similarly measured at the site of each plaque. Pivotal parameters for analysis were mean IMT (right, left, and mean of right and left) and maximum IMT (right, left, and thicker value of right and left) of the distal wall of the CCA in the above-mentioned 2-cm section.

Address for correspondence: Masatoshi Koga, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan
E-mail: koga@ncvc.go.jp
Received: June 21, 2017
Accepted for publication: September 19, 2017

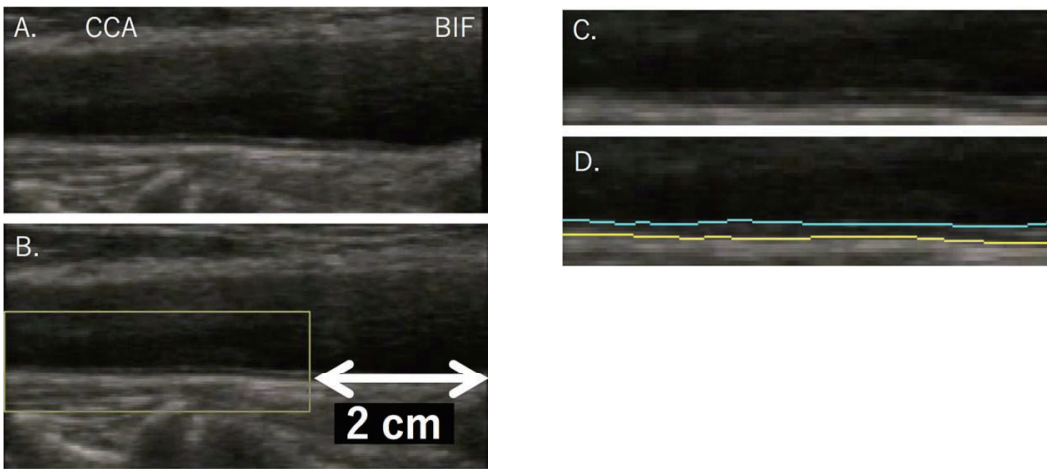

Fig. 1. B-mode ultrasound image sample of the CCA showing the measurement of IMT by IntimaScope

A. Still images (640 ×480 pixels) were imported from the videotapes or CD-Rs via a video port with a resolution of 1 pixel corresponding to 0.1 mm.
B. Measurement of a CCA section.
IMT measured using the long-axis view of each CCA. An image is obtained in the region including the far wall of the CCA between the tip of the bifurcation site and a point 2-cm proximal.
C. Standardized longitudinal B-mode of CCA.
D. Automated measurement of IMT from the far wall.
IMT is automatically calculated using a computer-assisted measurement system (IntimaScope; Mediacross, Tokyo, Japan).

Statistical Analysis

Baseline characteristics between the pravastatin and control groups and between the patients included in the J-STARS Echo Study and those not included in the J-STARS Echo Study were compared using the chi-square test, *t*-test, and Wilcoxon rank-sum test, as appropriate. The mean and maximum IMTs stratified by baseline characteristics were compared using non-paired *t*-test. Multivariable analyses to assess factors associated with mean and maximum IMTs were performed using stepwise multiple linear regression analysis with age, sex, weight, body mass index, diabetes mellitus (DM), smoking habit, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, categories of blood pressure, glomerular filtration, creatinine clearance, urinary protein, chronic kidney disease, subtype of stroke, size of responsible infarction, location of infarction vessel, carotid bruit, and atrial flutter/fibrillation as independent variables. In the stepwise multiple linear regression analysis, independent variables were selected by the method of predicted residual error sum of squares statistic. The factors used as variables for the stepwise multiple linear regression analysis are described in **Table 1**.

All analyses were performed using SAS software (Cary, NC, USA), and the level of significance was set at $p<0.05$ (two-tailed).

Results

Among the 123 participating sites in the main J-STARS study, 61 centers had certified sonographers available. From these 61 centers, 941 patients were enrolled in the main J-STARS study, and 864 patients agreed to participate in the J-STARS Echo Study between March 2004 and February 2009 (**Fig. 2**). Among the 864 patients, 71 patients did not undergo ultrasound evaluation. Thus, 793 patients were included in this study [530 men (66.8%), 66.4 ± 8.3 years old]. Of these 793 patients, 388 patients (49%) were assigned to receive pravastatin (pravastatin group), and 405 (51%) did not receive any statins (control group).

The baseline characteristics of the patients in this substudy and the remaining 796 patients in the J-STARS study were generally similar (**Supplementary Table 1**). **Table 1** shows the baseline characteristics of the patients in the pravastatin and control groups enrolled in the J-STARS Echo Study. There were no significant differences between the two groups, except for the baseline National Institutes of Health Stroke Scale (NIHSS) scores: median, 0 (IQR 0–2) vs. 1 (IQR 0–2), respectively ($p=0.02$).

Overall mean IMT was 0.89 ± 0.15 mm: 0.89 ± 0.15 mm in the pravastatin group and 0.89 ± 0.15

Table 1. Baseline characteristics

		Pravastatin group (*N*=388)	Control group (*N*=405)	*P* value
Age, y		66.4 ± 8.2	66.4 ± 8.4	0.96
Male		255 (65.7)	275 (67.9)	0.51
Height, cm		159.6 ± 8.8	159.7 ± 8.3	0.79
Weight, kg		60.8 ± 9.8	60.5 ± 10.0	0.64
Body mass index, kg/m^2		23.8 ± 2.9	23.7 ± 3.0	0.49
Blood pressure, mmHg*	SBP	136.5 ± 17.6	135.8 ± 16.9	0.56
	DBP	79.1 ± 11.7	78.5 ± 10.5	0.47
Risk factor	Hypertension	294 (75.8)	321 (79.3)	0.24
	Diabetes mellitus	89 (22.9)	107 (26.4)	0.26
	Coronary artery disease	15 (3.9)	20 (4.9)	0.46
	Smoking habit†	201 (51.8)	218 (53.8)	0.52
Medication	Lipid-lowering agents	28 (7.2)	40 (9.9)	0.18
	Antihypertensive	233 (60.1)	253 (62.5)	0.48
	Glucose-lowering agents	70 (18.0)	80 (19.8)	0.54
	Anti-thrombotics	356 (91.8)	369 (91.1)	0.75
Laboratory data, mg/dL‡	T-chol	211.8 ± 25.8	209.3 ± 25.4	0.18
	HDL-chol	53.8 ± 16.3	52.2 ± 14.8	0.17
	LDL-chol	130.9 ± 25.4	130.3 ± 24.5	0.74
	TG	139.7 ± 71.1	142.8 ± 70.7	0.54
	FBS	116.3 ± 39.0	115.8 ± 36.2	0.85
Subtype of stroke	Atherothrombotic infarction	93 (24.0)	102 (25.2)	0.99
	Lacunar infarction	251 (64.7)	275 (67.9)	
	Undetermined	44 (11.3)	28 (6.9)	
Size of infarction§	Small	302 (77.8)	297 (73.3)	0.22
	Medium	72 (18.6)	81 (20.0)	
	Large	2 (0.5)	8 (2.0)	
Location of infarction	Cortical artery	61 (15.7)	73 (18.0)	0.61
	Perforating artery	298 (76.8)	295 (72.8)	
	Both	17 (4.4)	18 (4.4)	
Responsible vessel‖	ACA	5 (1.3)	7 (1.7)	0.46
	MCA	241 (62.1)	267 (65.9)	
	PCA	30 (7.7)	24 (5.9)	
	VB	94 (24.2)	80 (19.8)	
	BZ	6 (1.5)	8 (2.0)	
Baseline NIHSS score, median**		0 (IQR 0-2)	1 (IQR 0-2)	0.02
Baseline mRS score††	0	123 (31.7)	130 (32.1)	0.58
	1	185 (47.7)	176 (43.5)	
	2	61 (15.7)	74 (18.3)	
	3	8 (2.1)	11 (2.7)	
	4	11 (2.8)	13 (3.2)	

n (%) or mean ± SD

*SBP: systolic blood pressure; DBP: diastolic blood pressure

†Smoking habit including current smoker and past smoker

‡T-chol: total cholesterol; HDL-chol: high density lipoprotein cholesterol; LDL-chol: low density lipoprotein cholesterol; TG: triglyceride; FBS: fasting blood sugar

§Size of infarction: small was defined as lesion within a diameter of 1.5 cm, large was defined as a lesion more than half of the cerebral lobe. Medium was defined as between small and large.

‖ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VB: vertebrobasilar artery; BZ: border zone

**NIHSS, National Institutes of Health Stroke Scale

††mRS, modified Rankin Scale

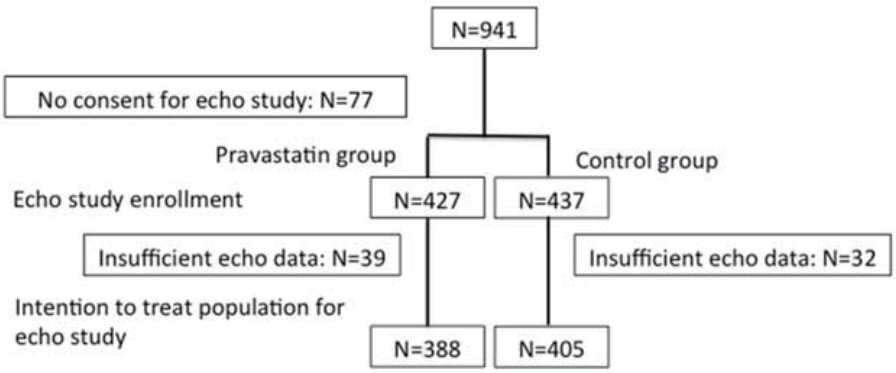

Fig. 2. Patient selection flow chart

Table 2. Baseline mean and maximum intima-media complex thickness

	Total	Pravastatin Group	Control Group	*P* value
Mean intima-media complex thickness, mm				
Left (mm)				
Mean ± SD	0.89 ± 0.18	0.89 ± 0.17	0.89 ± 0.18	0.98
Median, IQR	0.86, 0.77-0.98	0.87, 0.77-0.99	0.86, 0.78-0.98	
Right (mm)				
Mean ± SD	0.89 ± 0.16	0.89 ± 0.16	0.88 ± 0.15	0.91
Median, IQR	0.87, 0.78-0.97	0.87, 0.78-0.97	0.87, 0.78-0.96	
Average of both sides (mm)				
Mean ± SD	0.89 ± 0.15	0.89 ± 0.15	0.89 ± 0.15	0.99
Median, IQR	0.87, 0.78-0.97	0.87, 0.78-0.97	0.87, 0.78-0.96	
Maximum intima-media complex thickness, mm				
Left (mm)				
Mean ± SD	1.11 ± 0.29	1.11 ± 0.29	1.10 ± 0.29	0.59
Median, IQR	1.05, 0.92-1.22	1.06, 0.92-1.24	1.04, 0.93-1.19	
Right (mm)				
Mean ± SD	1.10 ± 0.29	1.10 ± 0.30	1.10 ± 0.27	0.74
Median, IQR	1.05, 0.93-1.19	1.05, 0.92-1.20	1.05, 0.93-1.18	
Thicker value of the two sides (mm)				
Mean ± SD	1.19 ± 0.32	1.20 ± 0.33	1.18 ± 0.31	0.56
Median, IQR	1.12, 0.98-1.29	1.13, 0.98-1.32	1.12, 0.98-1.27	

SD, standard deviation; IQR, interquartile range

mm in the control group ($p=0.99$). Overall maximum IMT was 1.19 ± 0.32 mm: 1.20 ± 0.33 mm in the pravastatin group and 1.18 ± 0.31 mm in the control group ($p=0.56$) (**Table 2**).

Table 3 shows relationships between baseline IMT and potentially associated factors in univariate analysis. Women, patients aged 65 years or older, category of blood pressure, hypertension, DM, smoking habit, HDL cholesterol less than 50 mg/ml, chronic kidney disease, and carotid bruit were positively associated with mean IMT. Stepwise multiple linear regression analysis included those factors that had differences in the univariate analysis. Age (per 10 years) ($p<0.001$), smoking habit ($p=0.004$), category of blood pressure ($p=0.006$), HDL cholesterol (per 10 mg/dl) ($p=0.008$), and DM ($p=0.010$) were selected and significantly associated with mean IMT (**Table 4**).

Similarly, women, patients aged 65 years or older, hypertension, DM, smoking habit, and HDL cholesterol less than 50 mg/ml were positively associated with maximum IMT in the univariate analysis. Age (per 10 years) ($p<0.001$), smoking habit ($p=$

Table 3. Baseline intima-media complex thickness by potentially associated factors

		N	Mean IMT (mm), mean ± SD	*P*-Value	Maximum IMT (mm), mean ± SD	*P* value
Age, years	< 65	326	0.86 ± 0.15	< 0.01	1.14 ± 0.29	< 0.01
	≥ 65	467	0.91 ± 0.15		1.22 ± 0.34	
Sex	Male	530	0.90 ± 0.15	0.01	1.21 ± 0.33	0.01
	Female	263	0.87 ± 0.16		1.15 ± 0.31	
Weight, kg	< 60	361	0.88 ± 0.16	0.11	1.18 ± 0.35	0.48
	≥ 60	430	0.90 ± 0.15		1.20 ± 0.30	
Body mass index, kg/m^2	< 24	421	0.88 ± 0.16	0.13	1.18 ± 0.35	0.2
	≥ 24	368	0.90 ± 0.15		1.21 ± 0.29	
Hypertension	Absent	178	0.84 ± 0.14	< 0.01	1.13 ± 0.31	0.01
	Present	615	0.90 ± 0.15		1.21 ± 0.32	
Diabetes mellitus	Absent	597	0.88 ± 0.15	0.01	1.17 ± 0.31	< 0.01
	Present	196	0.91 ± 0.16		1.25 ± 0.35	
Smoking habit	None	370	0.87 ± 0.15	0.02	1.16 ± 0.31	0.03
	Past	280	0.91 ± 0.15		1.22 ± 0.32	
	Current	139	0.89 ± 0.16		1.22 ± 0.36	
Total cholesterol, mg/dL	< 210	395	0.89 ± 0.15	0.62	1.20 ± 0.34	0.43
	≥ 210	395	0.89 ± 0.15		1.18 ± 0.31	
HDL cholesterol, mg/dL	< 50	384	0.91 ± 0.15	< 0.01	1.22 ± 0.30	< 0.01
	≥ 50	404	0.87 ± 0.16		1.16 ± 0.34	
LDL cholesterol, mg/dL	< 130	385	0.89 ± 0.15	0.77	1.19 ± 0.34	0.89
	≥ 130	397	0.89 ± 0.16		1.16 ± 0.31	
Triglyceride, mg/dL	< 130	414	0.88 ± 0.15	0.35	1.18 ± 0.33	0.65
	≥ 130	376	0.89 ± 0.15		1.20 ± 0.31	
Categories of blood pressure*	Category 1	83	0.91 ± 0.15	< 0.01	1.21 ± 0.30	0.18
	Category 2	274	0.91 ± 0.15		1.21 ± 0.31	
	Category 3	435	0.87 ± 0.15		1.17 ± 0.34	
eGFR, ml/min/1.73m^2 †	< 30	4	0.85 ± 0.16	0.09	1.21 ± 0.33	0.57
	30-59	187	0.90 ± 0.17		1.21 ± 0.33	
	≥ 60	60	0.88 ± 0.15		1.18 ± 0.32	
Creatinine clearance, ml/min	< 30	4	0.82 ± 0.16	0.25	1.17 ± 0.35	0.52
	30-59	183	0.90 ± 0.17		1.21 ± 0.39	
	≥ 60	604	0.88 ± 0.15		1.18 ± 0.30	
Urinary protein	Absent	689	0.89 ± 0.15	0.27	1.19 ± 0.33	0.63
	Present	83	0.91 ± 0.15		1.21 ± 0.31	
Chronic kidney disease	Absent	602	0.88 ± 0.15	0.04	1.18 ± 0.32	0.29
	Present	191	0.91 ± 0.16		1.21 ± 0.33	
Subtype of stroke	Atherothrombotic infarction	195	0.90 ± 0.16	0.51	1.21 ± 0.34	0.49
	Lacunar infarction	526	0.88 ± 0.15		1.18 ± 0.31	
	Other	72	0.89 ± 0.18		1.19 ± 0.35	
Size of infarction‡	None	27	0.86 ± 0.14	0.34	1.11 ± 0.26	0.56
	Small	599	0.88 ± 0.15		1.19 ± 0.32	
	Medium	153	0.90 ± 0.17		1.21 ± 0.36	
	Large	10	0.94 ± 0.14		1.20 ± 0.25	
Location of infarction	None	27	0.86 ± 0.14	0.49	1.11 ± 0.26	0.59
	Cortical artery	134	0.90 ± 0.16		1.20 ± 0.34	
	Perforating artery	593	0.89 ± 0.15		1.19 ± 0.33	
	Both	10	0.91 ± 0.13		1.20 ± 0.24	
Responsible vessel§	None	27	0.86 ± 0.14	0.71	1.11 ± 0.26	0.46
	ACA	12	0.89 ± 0.11		1.15 ± 0.17	
	MCA	508	0.89 ± 0.15		1.19 ± 0.30	
	PCA	54	0.86 ± 0,15		1.14 ± 0.36	
	VB-territory	174	0.90 ± 0.16		1.22 ± 0.39	
	Border Zone	14	0.89 ± 0.11		1.18 ± 0.19	
Carotid bruit	Absent	767	0.89 ± 0.15	0.04	1.19 ± 0.32	0.43
	Present	18	0.96 ± 0.20		1.25 ± 0.34	
Atrial flutter/fibrillation	Absent	775	0.88 ± 0.15	0.51	1.19 ± 0.32	0.16
	Present	10	0.92 ± 0.15		1.33 ± 0.34	

IMT, intima media complex thickness; SD, standard deviation; *Category 1: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; Category 2: SBP 140-159 mmHg or DBP 90-99 mmHg; Category 3: SBP < 140 mmHg and DBP<90 mmHg. †eGFR, estimated glomerular filtration rate ‡Size of infarction: Small was defined as a lesion within a diameter of 1.5 cm, large was defined as a lesion more than half of a cerebral lobe. Medium was defined between small and large. §ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; VB, vertebrobasilar artery

Table 4. Multiple regression analysis for mean intima-media complex thickness

Variable	Parameter Estimate	Standard Error	Pr>|t|
Age (/10 years)	0.044	0.007	<0.001
Smoking habit*	0.022	0.007	0.004
Category of blood pressure†	0.022	0.008	0.006
HDL cholesterol‡ (/10 mg/dL)	−0.009	0.003	0.008
Diabetes mellitus	0.033	0.013	0.010
Size of responsible lesion§	0.017	0.011	0.125

*Smoking habit including current smoker and past smoker
†Category of blood pressure: Category 1, SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; Category 2, SBP 140-159 mmHg or DBP 90-99 mmHg; Category 3, SBP < 140 mmHg and DBP < 90 mmHg
‡HDL-cholesterol: High density lipoprotein cholesterol
§Size of responsible lesion: small, medium, or large

Table 5. Multiple regression analysis for maximum intima-media complex thickness

Variable	Parameter Estimate	Standard Error	Pr>|t|
Age (/10 years)	0.076	0.014	<0.001
Smoking habit*	0.053	0.016	0.001
Diabetes mellitus	0.084	0.027	0.002
HDL cholesterol (/10 mg/dL)†	−0.016	0.007	0.036
Category of blood pressure‡	0.025	0.017	0.146

*Smoking habit including current smoker and past smoker
†HDL-cholesterol, High density lipoprotein cholesterol
‡Category 1: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; Category 2: SBP 140-159 mmHg or DBP 90-99 mmHg; Category 3: SBP < 140 mmHg and DBP < 90 mmHg

0.001), DM (p=0.002), and HDL cholesterol (p=0.036) were selected and significantly associated with maximum IMT in the stepwise multiple linear regression analysis (**Table 5**).

Discussion

The J-STARS Echo Study enrolled the largest sample size in Asia to assess the relationship between IMT progression and statin use, comparable to previous trials from Western countries. Baseline characteristics and contributing factors to the baseline mean and maximum IMTs were assessed in Japanese noncardioembolic stroke patients. Age, smoking habit, category of blood pressure, DM, and HDL cholesterol were independently related to the baseline mean IMT, and they were also related to the baseline maximum IMT, except for category of blood pressure.

Carotid IMT has been used to define atherosclerosis in a number of recent clinical trials for cardiovascular diseases and stroke. The relationship between IMT and statin use has been assessed in many studies and trials from Western countries, but there are few trials, with a small number of patients, from Asian countries. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial is the largest study, including 4731 patients who had a stroke or transient ischemic attack, which showed the effect of statin use on reduction in the risk of stroke. However, the SPARCL trial did not include carotid IMT as a clinical outcome[14]. The present study included the largest sample size of noncardioembolic stroke patients, examining the effect of statin on the progression of carotid IMT.

The Japanese population has been reported to have thinner carotid IMTs than Western populations, probably due to the differences in the lifetime period levels of obesity through adipocytokines or certain levels of inflammation through lipoprotein distribution, rather than differences in genetic factors[15-19]. Koreans and Japanese Americans have been found to have thicker IMTs than native Japanese, and this might explain such risk factors, rather than genetic factors, contributing to carotid IMT[15, 20]. **Supplementary Tables 2** and **3** show previous trials that reported the association between IM and statin use[6, 7, 21-26]. Interestingly, the baseline mean and maximum IMTs in the present study were similar to those from previous trials that examined the effects of statin therapy in Western and Asian countries (**Supplementary Table 2**).

Because this study focused on patients with a history of ischemic stroke and they had a high prevalence of atherosclerotic risk factors, such as aging, high blood pressure, and DM (**Supplementary Table 3**), carotid IMT assessed in the present study may be higher than that in other non-stroke-related Japanese populations[20, 27].

Age, smoking habit, category of blood pressure, DM, and HDL cholesterol were independently associated with mean IMT. These factors have been previously reported as atherosclerotic risk factors and have been strongly related to carotid IMT and atherothrombotic ischemic stroke[28-34]. However, the factors related to maximum IMT were somewhat different from those related to mean IMT in the present study; category of blood pressure was not significantly related to maximum IMT. This result may be due to different phenotypes of the atherosclerotic process between mean and maximum IMTs[35]. Mean IMT reflects the hypertensive hypertrophic response of the medial cells, which seems to be related to changes in local shear stress, and represents a part of arterial remodeling that occurs at the early stage of atherosclerosis[36-39], whereas maximum IMT often reflects plaques that mainly occur in the intima (endothelial cell, basal lamina, and subendothelial matrix), which represent the late stage of arteriosclerotic change related to inflammation, oxidation, endothelial dysfunction, and smooth muscle cell proliferation[40]. Given this pathophysiological difference, hypertension may not have a significant influence on maximum IMT.

LDL cholesterol, a well-known atherosclerotic risk factor[41, 42], was not significantly associated with mean and maximum IMTs in the present study, probably because enrolled patients had a limited range of total cholesterol (4.65–6.21 mmol/L) and relatively low LDL cholesterol levels compared with those in other trials (**Supplementary Table 3**). Recently, the ratio of LDL cholesterol/HDL cholesterol was indicated as a risk factor for atherosclerosis[43]. Further multivariable analyses with this ratio, instead of LDL cholesterol and HDL cholesterol, showed that this ratio was independently associated with both mean and maximum IMTs in this cohort (**Supplementary Tables 4** and **5**).

One of the limitations of this trial is that all enrolled patients for the main J-STARS trial were not randomized to the J-STARS Echo Study, because only patients from institutes that had certified sonographers were enrolled. However, baseline characteristics of enrolled patients in the J-STARS Echo Study were almost similar to those of non-enrolled patients (**Supplementary Table 1**). The relatively low statin dosage in this trial, compared with the dosage used worldwide, may also be a limitation. High-dose statin use is known to strongly suppress inflammation-related atherosclerotic factors, but there is still controversy regarding its efficacy and safety because of the small number of randomized, controlled trials involving statins[44].

Because there are scarce data regarding the relationship between IMT and statin use in patients with prior ischemic stroke, we examined this relationship in a large sample of Japanese noncardioembolic stroke patients. From this baseline data analyses, we showed factors associated with baseline IMTs and the similarity of baseline characteristics and IMTs between the pravastatin and control groups. We will examine the effect of the associated factors, such as age, smoking, category of blood pressure, HDL cholesterol, and DM, on the change in IMTs over 5 years of follow-up. Further observation of the relationship between statin use and sequential changes in IMT over 5 years will be conducted.

Conclusion

In the Japanese stroke patients recruited for the J-STARS Echo Study, the overall mean and maximum IMTs were 0.89 ± 0.15 mm and 1.19 ± 0.32 mm, respectively. Age, smoking, hypertension, HDL cholesterol, and DM were associated with mean IMT, and those, except for hypertension, were associated with maximum IMT.

Acknowledgments

We would like to thank the patients and their families involved in the present study, and we also appreciate the other study participants, physicians, supporting medical staff, and coworkers for their assistance in the preparation and execution of this study. The authors thank Mr.Hideki Kono and Ms. Yoko Nakagawa (Foundation for Biomedical Research and Innovation Translational Research Informatics Center) for their statistical analysis support, Drs. Tatsuo Kohriyama, Setsuro Ibayashi, and Manabu Inoue for their valuable advice, and Ms. Kie Yamaguchi (Clinical Research Nurses at the National Cerebral and Cardiovascular Center) for ultrasound assessments.

Sources of Funding

The present study was supported by a grant from the Ministry of Health, Labour and Welfare of Japan. After the period of governmental support expired, the study was conducted in collaboration with Hiroshima University Medical School and the Foundation of Bio-

medical Research and Innovation.

Disclosures

MK reports honoraria from Daiichi Sankyo Co., Ltd.; Bayer Healthcare; Boehringer Ingelhaeim GmbH; AstraZeneca; and Pfizer Inc. KT reports honoraria from Daiichi Sankyo Co., Ltd.; Bayer Healthcare; Boehringer Ingelhaeim GmbH; and Bristol-Myers Squibb. KM reports honoraria from Bayer Healthcare; Otsuka Pharmaceuticals; Boehringer Ingelhaeim GmbH; AstraZeneca; Pfizer Inc.; Mitsubishi Tanabe Pharma Cooperation; Japan Stryker; Kowa; Nihon Medi-Physics Co., Ltd.; Bristol-Myers Squibb; Sawai Pharmaceutical Co., Ltd.; Sumitomo Dainippon Pharma Co., Ltd.; Medico's Hirata Inc.; Daiichi Sankyo Co., Ltd.; Astellas Pharma Inc.; Kyowa Hakko Kirin Pharma; Sanofi S.A.; MSD Eisai Co., Ltd.; Nippon Chemiphar; and Towa Pharmaceutical Co., Ltd. MY reports grants and lecture fees from Daiichi Sankyo Co., LTD. NH reports honoraria from Mochida Pharmaceutical Co., Ltd. HO reports remuneration from Daiichi Sankyo Co., Ltd. HM reports speaker fees from Daiichi Sankyo, Otsuka Pharmaceutical, Eisai, Nihon Pharmaceutical Takeda Pharmaceutical, Boehringer Ingelheim, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Sanofi, Bayer, Kyowa Hakko Kirin, and Fuji Film, and Grants-in-Aid for Scientific Research (JP26293211) and research support from Eisai, Pfizer Takeda Pharmaceutical, Otsuka Pharmaceutical, Nihon Pharmaceutical, Shionogi, Teijin Pharma, Fuji Film, Boehringer Ingelheim, Nihon Medi-Physics, Bayer, MSD, Daiichi Sankyo, Kyowa Hakko Kirin, Novartis, and Mitsubishi Tanabe Pharma. KK reports grants and honoraria from Daiichi Sankyo Co., Ltd.; Bayer Healthcare; Otsuka Pharmaceuticals; Boehringer Ingelheim GmbH; AstraZeneca; and Sumitomo Dainippon Pharma Co., Ltd. and honoraria from Sanofi K.K.; Eisai Co., Ltd.; and Kyowa Hakko Kirin Pharma. SU reports honoraria from Daiichi Sankyo Co., Ltd.; Astellas Pharma Inc.; and Kowa Hakko Kirin. MM reports grants from Takeda Pharmaceutical Co., Ltd.; Sanofi K.K.; Mochida Pharmaceutical Co., Ltd.; Otsuka Pharmaceutical; and Daiichi Sankyo Co., Ltd. and honoraria from Sanofi K.K.; Byer Healthcare; and Daiichi Sankyo Co., Ltd. Other authors had no conflicts of interest.

References

1) Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid Intima-Media T hickness for Atherosclerosis. J Atheroscler Thromb. 2016; 23: 18-31
2) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340: 14-22
3) Crouse JR 3rd, Craven TE, Hagaman AP, Bond MG. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation. 1995; 92: 1141-1147
4) Probstfield JL, Margitic SE, Byington RP, Espeland MA, Furberg CD. Results of the primary outcome measure and clinical events from the Asymptomatic Carotid Artery Progression Study. Am J Cardiol. 1995; 76: 47C-53C
5) Salonen RM. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. Circulation. 2003; 107: 947-953
6) Mercuri M, Bond MG, Sirtori CR, Veglia F, Crepaldi G, Feruglio FS, Descovich G, Ricci G, Rubba P, Mancini M, Gallus G, Bianchi G, D'Alò G, Ventura A. Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic Mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. Am J Cardiol. 1996; 101: 627-634
7) MacMahon S, Sharpe N, Gamble G, Hart H, Scott J, Simes J, White H. Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID Atherosclerosis Substudy. LIPID Trial Research Group. Circulation. 1998; 97: 1784-1790
8) Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, Kashiwagi S, Hayashi J. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia: Fukuoka Atherosclerosis Trial (FAST). J Am Coll Cardiol. 2002; 39: 610-616
9) Nagai Y, Metter EJ, Earley CJ, Kemper MK, Becker LC, Lakatta EG, Fleg JL. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation. 1998; 98: 1504-1509
10) Nagai Y, Kohriyama T, Origasa H, Minematsu K, Yokota C, Uchiyama S, Ibayashi S, Terayama Y, Takagi M, Kitagawa K, Nomura E, Hosomi N, Ohtsuki T, Yamawaki T, Matsubara Y, Nakamura M, Yamasaki Y, Mori E, Fukushima M, Kobayashi S, Shinohara Y, Yamaguchi T, Matsumoto M, J-STARS Investigators. Rationale, design, and baseline features of a randomized controlled trial to assess the effects of statin for the secondary prevention of stroke: the Japan Statin Treatment Against Recurrent Stroke (J-STARS). International Journal of Stroke. 2014; 9: 232-239
11) Toyoda K, Minematsu K, Yasaka M, Nagai Y, Hosomi N, Origasa H, Kitagawa K, Uchiyama S, Koga M, Matsumoto M, J-STARS Investigators. The Japan Statin Treatment Against Recurrent Stroke (J-STARS) Echo Study: Rationale and trial protocol. J Stroke Cerebrovasc Dis. 2017; 26: 595-599
12) Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media

thickness and plaque consensus (2004−2006−2011). Cerebrovasc Dis. 2012; 34: 290-296
13) Yanase T, Nasu S, Mukuta Y, Shimizu Y, Nishihara T, Okabe T, Nomura M, Inoguchi T, Nawata H. Evaluation of a new carotid intima-media thickness measurement by B-mode ultrasonography using an innovative measurement software, intimascope. Am J Hypertens. 2006; 19: 1206-1212
14) Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006; 355: 549-559
15) Choo J, Ueshima H, Jang Y, Sutton-Tyrrell K, El-Saed A, Kadowaki T, Takamiya T, Okamura T, Ueno Y, Nakamura Y, Sekikawa A, Curb JD, Kuller LH, Shin C. Difference in carotid intima-media thickness between Korean and Japanese men. Ann Epidemiol. 2008; 18: 310-315
16) Sekikawa A, Ueshima H, Kadowaki T, El-Saed A, Okamura T, Takamiya T, Kashiwagi A, Edmundowicz D, Murata K, Sutton-Tyrrell K, Maegawa H, Evans RW, Kita Y, Kuller LH. Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. Am J Epidemiol. 2007; 165: 617-624
17) Matsuzawa Y. White adipose tissue and cardiovascular disease. Best Pract Res Clin Endocrinol Metab. 2005; 19: 637-647
18) Tiong AY, Brieger D. Inflammation and coronary artery disease. Am Heart J. 2005; 150: 11-18
19) Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation. 2004; 109: Iii2-Iii7
20) Handa N, Matsumoto M, Maeda H, Hougaku H, Kamada T. Ischemic stroke events and carotid atherosclerosis. Results of the Osaka Follow-up study for Ultrasonographic Assessment of Carotid Atherosclerosis (the OSACA Study). Stroke. 1995; 26: 1781-1786
21) Furberg CD, Adams HP, Jr., Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation. 1994; 90: 1679-1687
22) Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML: METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007; 297: 1344-1353
23) Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, Putter H, Huisman MV. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. Diabetes Care. 2004; 27: 2887-2892
24) Nohara R, Daida H, Hata M, Kaku K, Kawamori R, Kishimoto J, Kurabayashi M, Masuda I, Sakuma I, Yamazaki T, Yokoi H, Yoshida M; Justification for Atherosclerosis Regression Treatment (JART) Investigators. Effect of intensive lipid-lowering therapy with rosuvastatin on progression of carotid intima-media thickness in Japanese patients: Justification for Atherosclerosis Regression Treatment (JART) study. Circ J. 2012; 76: 221-229
25) Kim KH, Cho SH, Yim YR, Lee KJ, Yum JH, Yoon HJ, Yoon NS, Hong YJ, Park HW, Kin JH, Ahn Y, Jeong MH, Cho JG, Park JC. Effects of low dose versus high dose statin therapy on the changes of endothelial function and carotid intima-media thickness in patients with variant angina. J Cardiovasc Ultrasound. 2013; 21: 58-63
26) Ishigaki Y, Kono S, Katagiri H, Oka Y, Oikawa S; NTTP investigators. Elevation of HDL-C in response to statin treatment is involved in the regression of carotid atherosclerosis. J Atheroscler Thromb. 2014; 21: 1055-1065
27) Kadota A, Miura K, Okamura T, Fujiyoshi A, Ohkubo T, Kadowaki T, Takashima N, Hisamatsu T, Nakamura Y, Kasagi F, Maegawa H, Kashiwagi A, Ueshima H; SESSA Research Group; NIPPON DATA80/90 Research Group. Carotid intima-media thickness and plaque in apparently healthy Japanese individuals with as estimated 10-year absolute risk of CAD death according to the Japan Atherosclerosis Society (JAS) guidelines 2012: the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). J Atheroscler Thromb. 2013; 20: 755-766
28) Watanabe H, Yamane K, Fujikawa R, Okubo M, Egusa G, Kohno N. Westernization of lifestyle markedly increases carotid intima-media wall thickness (IMT) in Japanese people. Atherosclerosis. 2003; 166: 67-72
29) Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol. 1991; 134: 250-256
30) Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke. 1994; 25: 66-73
31) Kim DS, Burt AA, Ranchalis JE, Jarvik LE, Eintracht JF, Furlong CE, Jarvik GP. Effects of dietary components on high-density lipoprotein measures in a cohort of 1,566 participants. Nutr Metab. 2014; 11: 1
32) Nagai Y, Kitagawa K, Yamagami H, Kondo H, Hougaku H, Hori M, Matsumoto M. Carotid artery intima-media thickness and plaque score for the risk assessment of stroke subtypes. Ultrasound Med Biol. 2002; 28: 1239-1243
33) Notsu Y, Yano S, Takeda M, Yamasaki M, Isomura M, Nabika T, Nagai A. Association of high-Density Lipoprotein Subclasses with Carotid Intima-Media Thickness: Shimane CoHRE Study. J Atheroscler Thromb. 2017; Apr 27. Doi: 10.5551/jat.38844. [Epub ahead of print] Pubmed PMID: 28450678
34) Zhong C, Xia W, Zhong X, Xu T, Li H, Zhang M, Wang A, Xu T, Sun Y, Zhang Y. Lipid Accumulation Product and Hypertension Related to Stroke: a 9.2-Year Prospective Study Among Mongolian in China. J Atheroscler Thromb. 2016; 23: 830-838
35) Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary

and cerebrovascular disease. Curr Cardiol Rep. 2009; 11: 21-27
36) Baldassarre D, Porta B, Camera M, Amato M, Arquati M, Brusoni B, Fiorentini C, Montorsi P, Romano S, Veglia F, Tremoli E, Cortellaro M; MIAMI Study Group. Markers of inflammation, thrombosis and endothelial activation correlate with carotid IMT regression in stable coronary disease after atorvastatin treatment. Nutr Metab Cardiovasc Dis. 2009; 19: 481-490
37) Polak JF, Pencina MJ, Meisner A, Pencina KM, Brown LS, Wolf PA, D'Agostino RB Sr. Associations of carotid artery intima-media thickness (IMT) with risk factors and prevalent cardiovascular disease comparison of mean common carotid artery IMT with maximum internal carotid artery IMT. J Ultrasound Med. 2010; 29: 1759-1768
38) Zhao W, Wu Y, Shi M, Bai L, Tu J, Guo Z, Jiang R, Zhang J, Ning X, Wang J. Sex differences in prevalence of and risk factors for carotid plaque among adults: A population-based cross-sectional study in rural China. Sci Rep. 2016; 6: 38618
39) Touboul PJ, Labreuche J, Bruckert E, Schargrodsky H, Prati P, Tosetto A, Hernandez-Hernandez R, Woo KS, Silva H, Vicaut E, Amarenco P. HDL-C, triglycerides and carotid IMT: a meta-analysis of 21,000 patients with automated edge detection IMT measurement. Atherosclerosis. 2014; 232: 65-71
40) Hegele RA. The pathogenesis of atherosclerosis. Clin Chim Acta. 1996; 246: 21-38
41) Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy- Thrombolysis in Myocardial Infarction 22 Investigators. Intensive vursus moderate lipid lowering with statins after acute coronary sydromes. N Engl J Med. 2004; 350: 1495-1504
42) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352: 1425-1435
43) Fujihara K, Suzuki H, Sato A, Kodama S, Heianza Y, Saito K, Iwasaki H, Kobayashi K, Yatoh S, Takahashi A, Yamada N, Sone H, Shimano H. Carotid artery plaque and LDL-to-HDL cholesterol ratio predict atherosclerotic status in coronary arteries in asymptomatic patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2013; 20: 452-464
44) Collins R, Reith C, Emberson, J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016; 388: 2532-2561

Supplementary Table 1. Baseline characteristics of patients who were and were not included in the J-STARS Echo Study

		Included in J-STARS Echo Study (*N*=793)	Not included in J-STARS Echo Study (*N*=785)	*P*-Value
Age, years		66.4 ± 8.3	66.0 ± 8.6	0.32
Male		530 (66.8)	557 (71.0)	0.08
Height, cm		159.7 ± 8.5	160.9 ± 8.8	< 0.01
Weight, kg		60.6 ± 9.9	61.6 ± 10.3	0.07
Body mass index, kg/m^2		23.7 ± 3.0	23.7 ± 3.2	0.95
Blood pressure, mmHg*	SBP	136.2 ± 17.3	138.1 ± 18.3	0.03
	DBP	78.8 ± 11.1	79.9 ± 11.5	0.06
Risk factor	Hypertension	615 (77.6)	585 (74.5)	0.16
	Diabetes mellitus	196 (24.7)	173 (22.0)	0.21
	Coronary artery disease	35 (4.4)	46 (5.9)	0.17
	Smoking habit	419 (52.8)	427 (54.4)	0.31
Medication	Lipid-lowering agents	68 (8.6)	50 (6.4)	0.10
	Antihypertensive	486 (61.3)	467 (59.5)	0.55
	Glucose-lowering agents	150 (18.9)	142 (18.1)	0.70
	Anti-thrombotics	725 (91.4)	713 (90.8)	0.86
Laboratory data, mg/dL†	T-chol,	210.5 ± 25.5	209.6 ± 23.2	0.47
	HDL-chol,	53.0 ± 15.5	53.9 ± 16.0	0.23
	LDL-chol,	130.6 ± 24.9	128.2 ± 23.9	0.05
	TG,	141.3 ± 70.9	143.3 ± 77.5	0.63
	FBS,	116.0 ± 37.6	119.2 ± 44.1	0.12
Subtype of stroke	Atherothrombotic	195 (24.6)	206 (26.2)	0.22
	Lacunar	526 (66.3)	480 (61.1)	
	Undetermined	72 (9.1)	99 (12.6)	
Size of infarction‡	Small	599 (75.5)	573 (73.0)	0.16
	Medium	153 (19.3)	177 (22.5)	
	Large	10 (1.3)	9 (1.1)	
Location of infarction	Cortical	134(16.9)	158 (20.1)	0.27
	Perforating	593 (74.8)	566 (72.1)	
	Both	35 (4.4)	35 (4.4)	
Responsible vessel§	ACA	12 (1.5)	20 (2.5)	< 0.01
	MCA	508 (64.1)	439 (55.9)	
	PCA	54 (6.8)	66 (8.4)	
	VB	174 (21.9)	205 (26.1)	
	BZ	14 (1.8)	29 (3.7)	
Baseline NIHSS score ‖, median		1.0 (IQR0-2)	1.0 (IQR0-2)	0.05
Baseline mRS score**	0	253 (31.9)	294 (37.5)	0.02
	1	361 (45.5)	321 (40.9)	
	2	135 (17.0)	120 (15.3)	
	3	19 (2.4)	22 (2.9)	
	4	24 (3.0)	13 (1.7)	

n (%) or Mean ± SD

*SBP: systolic blood pressure, DBP: diastolic blood pressure

†T-chol: total cholesterol, HDL-chol: high density lipoprotein cholesterol, LDL-chol: low density lipoprotein cholesterol, TG: triglyceride, FBS: fasting blood sugar

‡Size of infarction: small was defined as lesion within diameter 1.5 cm, large was defined as lesion more than half of cerebral lobe. Medium was defined as between small and large.

§ACA: anterior cerebral artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, VB: vertebrobasilar artery, BZ: border zone

‖ National Institutes of Health Stroke Scale

**modified Rankin Scale

Supplementary Table 2. Carotid intima-media complex thickness in the present and previous studies

Study	Year	Mean IMT, mm	Maximum IMT, mm
ACAPS[12]	1994	1.14 ± 0.19	NA
CAIUS[5]	1996	0.88 ± 0.18	NA
LIPID[6]	1998	0.80 ± 0.01 / 0.79 ± 0.01*	NA
Beishiuizen, ED[14]	2004	0.78 ± 0.13 / 0.76 ± 0.12†	NA
METEOR[13]	2007	0.76 ± 0.12	1.15 ± 0.19
JART[15]	2012	0.92 ± 0.22 / 0.87 ± 0.19‡	1.66 ± 0.59 / 1.61 ± 0.52‡
Kim, KH[16]	2013	0.61 ± 0.06 / 0.60 ± 0.06§	NA
Ishigaki, Y[17]	2014	0.86 ± 0.25 / 0.91 ± 0.30‖	1.26 ± 0.76 / 1.30 ± 0.58‖
J-STARS	2016	0.89 ± 0.15	1.19 ± 0.32

IMT: intima media thickness; NA: not available
*Pravastatin group / Placebo group
†Cerivastatin group / Placebo group
‡Rosuvastatin / Pravastatin group
§Atorvastatin10mg group / Atorvastatin 40 mg group
‖Pitavastatin group / Pravastatin group

Supplementary Table 3. Patient characteristics of previous studies

	ACAPS	CAIUS	LIPID	Beishiuizen	METEOR	JART	KIM, K.H	Ishigaki, Y	J-STARS
Year	1994	1996	1998	2004	2007	2012	2013	2014	2016
Country*	USA	Italy	Australia, NZ	Netherland	USA, Europe	Japan	Korea	Japan	Japan
Study design	Lovastatin vs Placebo	Pravastatin vs Placebo	Pravastatin vs Placebo	Cerivastatin vs Placebo	Rosuvastatin vs Placebo	Rosuvastatin vs Pravastatin	Atorvastatin 10 mg vs 40 mg	Pitavastatin vs Pravastatin	Pravastatin vs No statin
N	919	305	522	250	982	314	70	97	793
Age (years)	61.7 ± 8.3	55.0 ± 6.0	61.0	**58.2 ± 11.4 / 58.8 ± 11.3	**57.0 ± 6.2 / 57.0 ± 6.0	**63.9 ± 8.9 / 63.3 ± 9.1	**54.2 ± 12.5 / 52.6 ± 9.8	**59.0 ± 8.8 / 60.0 ± 9.6	66.4 ± 8.3
Male (%)	51.5	53.0	88.0	47.2	**60.0/59.0	**49.7/49.0	**45.7/48.6	**41.2/52.2	68.9
BMI (kg/m^2)†	26.3 ± 9.6 / 25.4 ± 4.6	24.7 ± 2.6	-	31.0 ± 6.0 / 31.0 ± 6.3	**27.1 ± 4.0 / 27.5 ± 4.0	-	**24.3 ± 2.9 / 24.9 ± 3.9	**25.4 ± 4.5 / 26.0 ± 3.7	23.8 ± 3.0
Systolic BP (mmHg)‡	130.6 ± 17.1	133.6 ± 12.4	-	-	**124.0 ± 13.4 / 125.0 ± 13.6	**132.4 ± 17.0 / 130.0 ± 18.0	-	**136.3 ± 18.0 / 134.1 ± 17.2	136.2 ± 17.3
Diastolic BP (mmHg)‡	76.6 ± 8.9	81.3 ± 7.5	-	-	**77.0 ± 8.2 / 78.0 ± 8.5	**76.7 ± 11.1 / 74.9 ± 13.5	-	**75.9 ± 11.6 / 77.6 ± 10.1	78.8 ± 11.1
Hypertension (%)	28.8	-	-	50.4	-	**64.2/66.5	**17.1 / 14.3	**40.0 / 40.0	77.6
Diabetes mellitus (%)	2.3	-	5.0	-	-	**44.0/43.9	**5.7 / 8.6	-	24.7
CAD (%)§	-	-	75.0	-	-	**16.4/14.8	100	**2.0 / 0	4.4
Smoking habit									
Current (%)	11.9	24.0	-	24.4	-	**18.9/20.0	**37.1 / 28.6	**18.0 / 24.0	17.5
Former (%)	44.6	-	-	-	-	-	-	-	35.3
Never (%)	43.6	-	-	-	-	-	-	-	46.7
T-chol (mg/dl)‖	235.3 ± 23.2	261.4 ± 23.6	**207.3 / 220.8	**216.6 ± 29.8 / 212.3 ± 27.8	**229 ± 28.7 / 230 ± 27.7	-	**188.8 ± 39.9 / 191.9 ± 34.0	**244.8 ± 29.7 / 242.2 ± 34.3	210.5 ± 25.5
HDL-chol, (mg/dl)‖	**45.8 ± 11.6 / 58.3 ± 34.8	52.6 ± 11.6	**36.7 / 36.3	**46.8 ± 14.3 / 47.6 ± 15.1	**50 ± 9.0 / 49 ± 9.2	**54.2 ± 12.1 / 54.8 ± 13.2	**52.9 ± 13.2 / 51.4 ± 8.5	**54.2 ± 12.8 / 51.9 ± 9.6	53.0 ± 15.5
LDL-chol, (mg/dl)‖	155.6 ± 15.5	181.4 ± 19.7	**149.7 / 155.5	**137.2 ± 27.5 / 133.0 ± 27.5	**155 ± 24.1 / 154 ± 24.2	**163.8 ± 30.9 / 165.1 ± 29.1	**127.5 ± 36.9 / 127.9 ± 31.1	**163.4 ± 27.9 / 159.7 ± 25.6	130.6 ± 24.9
TG, (mg/dl)‖	318.8 ± 150.6	137.3 ± 49.6	**157.7 / 146.1	**166.5 ± 70.0 / 161.2 ± 70.0	**126 ± 64.3 / 134 ± 67.8	**149.6 ± 80.3 / 136.1 ± 69.8	**129.7 ± 42.8 / 144.6 ± 54.2	**147.4 ± 80.8 / 153.4 ± 88.1	141.3 ± 70.9
	**Men /Women		**Pravastatin /Placebo	**Cerivastatin /Placebo	**Rosuvastatin /Placebo	**Rosuvastatin /Pravastatin	**Atorvastatin 10 mg / 40 mg	**Pitavastatin /Pravastatin	

Mean (± Standard Deviation) or %

*USA: United States of America; NZ: New Zealand. †BMI: Body mass index. ‡BP: blood pressure. §CAD: Coronary artery disease. ‖T-chol: Total cholesterol, HDL-chol: High density lipoprotein cholesterol, LDL-chol: Low density lipoprotein cholesterol, TG: triglyceride.

Supplementary Table 4. Multiple regression analysis for mean intima-media complex thickness including LDL-cholesterol/ HDL-cholesterol and excluding LDL-cholesterol and HDL-cholesterol

Variable	Parameter Estimate	Standard Error	Pr>|t|
Age (/10 years)	0.044	0.007	<0.001
LDL-cholestrol/HDL-cholesterol*	0.022	0.006	0.001
Smoking habit†	0.022	0.007	0.003
Category of blood pressure‡	0.022	0.008	0.006
Diabetes mellitus	0.035	0.013	0.006

*LDL-cholesterol: Low density lipoprotein cholesterol, HDL-cholesterol: High density lipoprotein cholesterol
†Smoking habit including current smoker and past smoker
‡Category of blood pressure: Category 1, SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; Category 2, SBP 140-159 mmHg or DBP 90-99 mmHg; Category 3, SBP < 140 mmHg and DBP < 90 mmHg

Supplementary Table 5. Multiple regression analysis for maximum intima-media complex thickness including LDL-cholesterol/ HDL-cholesterol and excluding LDL-cholesterol and HDL-cholesterol

Variable	Parameter Estimate	Standard Error	Pr>|t|
Age (/10 years)	0.077	0.014	<0.001
Smoking habit*	0.053	0.016	0.001
Diabetes mellitus	0.087	0.027	0.001
LDL-cholestrol/HDL-cholesterol†	0.035	0.014	0.011
Category of blood pressure‡	0.026	0.017	0.137

*Smoking habit including current smoker and past smoker
†LDL-cholesterol: Low density lipoprotein cholesterol, HDL-cholesterol: High density lipoprotein cholesterol
‡Category 1: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; Category 2: SBP 140-159 mmHg or DBP 90-99 mmHg; Category 3: SBP < 140 mmHg and DBP < 90 mmHg